Depth of Anesthesia: Clinical Applications, Awareness, and Beyond

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A fundamental component of general anesthesia is unconsciousness. Patients consenting to general anesthesia do so with the expectation that they will not see, hear, feel, or remember intraoperative events. Recently, there has been increased public concern regarding intraoperative awareness, and studies show that a large percentage of patients who undergo general anesthesia report preoperative fears of awareness or recall (1).

In the past, conventional monitoring of anesthetic depth has included rudimentary signs such as patient movement, autonomic changes, and subjective clinical instinct. A considerable effort has been devoted to establishing a monitor that will reliably determine a patient's depth of anesthesia. Several different methods have been evaluated, yet none are 100% effective. At present there are at least two inherent obstacles in the development of a "foolproof" monitor of anesthetic depth. The first is that at present we have not yet comprehensively validated a unitary mechanism of general anesthesia. The second concerns the fact that general anesthesia occurs on a continuum without a quantitative dimension, and there is considerable interpatient and interanesthetic variability. Attempting to translate a conscious or unconscious state into a quantitative number can at best be limited to the practice of probability (Fig. 1).

Depth of anesthesia is dependent on the balance between two antagonistic factors: the anesthetic dose and surgical stimulation. Optimal depth of anesthesia requires a sufficient amount of anesthetic to achieve and maintain unconsciousness without compromising vital organ function. It is a tenet of anesthesiology dogma that the quantitative pharmacodynamic effect of a given dose of an anesthetic cannot be absolutely predicted in a specific patient. Accordingly, the dilemma for the anesthesiologist is—give too small an anesthetic dose and the patient may experience intraoperative recall, while too large an anesthetic dose may convey risk to the patient (e.g., decrease organ perfusion) and increase the incidence of troublesome side effects (e.g., delayed awakening). The optimal depth of anesthesia depends on balancing multiple anesthetic goals in the best interests of the patient. These goals include:

1. Avoid intraoperative awareness (4)
2. Optimize quality of recovery (5,6)
3. Maintain optimal hemodynamics
4. Avoid postoperative neurocognitive dysfunction
5. Avoid postoperative mortality (7–9)

Strategies utilized are part of the overall medical plan that balances risk of awareness against the risks of physiologic instability and postoperative complications.

This presentation will emphasize depth of anesthesia as it pertains to the risk of intraoperative awareness, including a summary of the recent ASA Practice Advisory on Intraoperative Awareness and Brain Function Monitoring. In addition, we will consider other data (some of which has yet to fully mature) regarding depth of anesthesia on fast tracking, postoperative neurocognitive dysfunction, and postoperative mortality. It is unfortunate, but some risk of intraoperative awareness must be realized in the year 2006 to avoid greater complications from excessively deep levels of anesthesia in some patient groups.

INTRAOPERATIVE AWARENESS

Incidence and Sequelae of Awareness

Memory consists of explicit or conscious memory, and implicit or unconscious memory. Explicit memory refers to the conscious recollection of previous experiences and is equivalent to remembering. Awareness during anesthesia describes conscious recall (explicit memory) of intraoperative events. However, many more anesthetized patients may respond to commands, yet lack conscious recall of intraoperative events.

The incidence of awareness is greater than most practitioners believe as the incidence is best estimated by formally interviewing patients postoperatively. Patients may not voluntarily report awareness if they were not disturbed by it. In addition, memory for awareness may be delayed. Only one-third of cases of awareness were identified before they left the postanesthesia care unit (10). One-third of the cases of awareness were not reported until 1–2 weeks postoperatively. A structured interview is therefore used to evaluate the incidence of awareness.

When a structured interview is used, it is found that intraoperative awareness occurs with surprising frequency. A prospective evaluation of awareness in nearly 12,000 patients undergoing general anesthesia

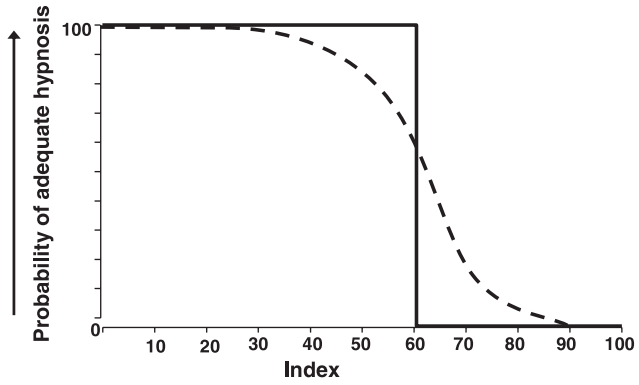

Figure 1. The solid line is the ideal probability curve with 100% sensitivity and specificity. The dashed line is a more realistic expectation of monitoring where a progressive decrease of the monitored index value correlates with increased probability of adequate hypnosis. Contemporary monitoring for intraoperative awareness should not be expected to have 100% sensitivity and specificity, but rather to assess the probability of an adequate depth of anesthesia. Indeed there have been case reports of patients experiencing intraoperative awareness in spite of monitored values indicating an adequate depth of anesthesia (2,3).

conducted in Sweden revealed an incidence of awareness of 0.18% in cases in which neuromuscular blocking drugs were used and 0.10% in the absence of such drugs (10). A similar incidence (1 per 1000 patients) has recently been observed in the United States in tertiary care centers, with a higher proportion among patients with co-existing morbidity (11). The incidence is higher with light anesthesia, such as obstetric cases (0.4%) and cardiac surgery (1.1%–1.5%).

Anesthetic technique is important in the pathogenesis of awareness during anesthesia. Several case reports and small clinical studies have suggested that intraoperative awareness is more likely to occur during anesthetics based on nitrous oxide and IV agents, and is less likely to occur when potent volatile anesthetics are used (12). Isoflurane in concentrations of $\geq$0.6 MAC prevented conscious recall and unconscious learning in anesthetized patients (13,14).

The most common causes of intraoperative awareness include light anesthesia, increased anesthetic requirement, or machine malfunction or misuse resulting in an inadequate anesthesia delivery (12). Light anesthesia may be necessary for physiologic stability in hypovolemic patients or those with limited cardiac reserve. ASA 3–5 patients undergoing major surgery had a higher incidence of awareness (11). Patients with awareness were more likely to have impaired cardiovascular status, undergo emergency surgery, receive lower doses of volatile anesthetics, and have more technical difficulties with anesthesia (15). Neuromuscular blockade prevents the most common sign of light anesthesia, patient movement. An inadequately anesthetized, nonparalyzed patient usually moves before experiencing recall, as lower anesthetic concentrations are needed to prevent awareness than to render immobility. Some patients, such as those using alcohol, opiates, amphetamines, and cocaine may require an increase in anesthetic dose. In addition, equipment problems with the vaporizer or IV infusion devices may lead to awareness, although these are less common causes of awareness, especially with use of end-tidal anesthetic gas analysis. In contrast to conventional clinical wisdom, most cases of awareness are not associated with hypertension and tachycardia (15,16). In fact, patients with awareness were more likely to have intraoperative hypotension requiring vasopressors (15).

Awareness during general anesthesia is a frightening experience, which may result in serious emotional injury and posttraumatic stress disorder (17). Patients who experienced awareness and recall during anesthesia most commonly described auditory perceptions, the sensation of paralysis, anxiety, helplessness, and panic. The sensation of pain occurs less frequently. Up to 70% of patients who had intraoperative awareness experience unpleasant after-effects, including sleep disturbances, dreams and nightmares, and flashbacks and anxiety during the day. Some patients develop posttraumatic stress disorder associated with repetitive nightmares, anxiety, irritability, and preoccupation with death. The predisposing factors for development of posttraumatic stress disorder are unknown, although many patients have underlying psychological disorders, especially depression. Most patients fail to inform their anesthesiologist that they experienced intraoperative recall. This is unfortunate because acknowledgment of what happened and prompt referral to psychological therapy may reduce the likelihood of long-term emotional sequelae.

In the past, awareness has not been a major medical liability problem in the United States, accounting for only 2% of claims in the ASA Closed Claims database (16). However, in the United Kingdom, one of eight of malpractice claims against anesthesiologists related to allegations of awareness during general anesthesia (17). Closed malpractice claims for awareness from the 1990s had a similar proportion of payments made to the plaintiff (52%) and similar payment amounts (median = $33,599) as in previous decades (18). Awareness may be a more substantial liability concern for cardiac anesthesiologists, as cardiac procedures accounted for 23% of awareness claims compared with 6% of all other general anesthesia claims in the 1990s (18). With the development of brain function monitoring coupled with prominent media coverage, awareness is likely to become a significant liability burden for all anesthesiologists in the future. Even in the 1990s, some high awards ($840,000) were made for sequelae of intraoperative awareness.

Prevention of Awareness

Published suggestions for the prevention of awareness include premedication with an amnesic agent, giving adequate doses of induction agents, avoiding

muscle paralysis unless totally necessary, supplementing opioid and N_2O anesthesia with ≥0.6 MAC of a volatile agent, administering 0.8–1.0 MAC when only volatile agents are used, adding amnesic agents when light anesthesia may be employed, and confirming the delivery of anesthetic agents to the patient (13). Monitoring of end-tidal levels of volatile anesthetics has been suggested to insure delivery of adequate levels of volatile anesthetics. Hypertension and tachycardia do not reliably predict awareness (13,17).

The JCAHO Sentinel Alert, issued October 6, 2004, contains suggestions for preventing and managing intraoperative awareness (19). Their recommendations included the development and implementation of an anesthesia awareness policy, including staff education, informed consent for high-risk patients, and timely maintenance of anesthesia equipment. Also advised were postoperative follow-up of all patients who have undergone general anesthesia and postoperative counseling for patients with awareness.

Brain Function Monitoring

In general, devices that monitor brain electrical activity for the purpose of assessing depth of anesthesia record electroencephalographic (EEG) activity. Some process spontaneous EEG and electromyographic activity and others measure evoked responses to auditory stimuli. These devices were reviewed in detail by the ASA Practice Advisory for Intraoperative Awareness and Brain Function Monitoring (20). Most of the research concerning depth of anesthesia and all of the research concerning awareness has been performed with the Bispectral Index (BIS®, Aspect Medical Systems) monitor.

Bispectral index uses a proprietary algorithm to convert a single channel of frontal EEG into an index of hypnotic level, ranging from 100 (awake) to zero (isoelectric EEG). Specific ranges (40–60) reflect a low probability of consciousness during general anesthesia. Newer versions of the monitor have included revised algorithms to suppress artifacts. In general, BIS performs best to predict response to verbal commands during sedation with propofol (21). A number of other events (cerebral ischemia or hypoperfusion), other drugs (muscle relaxants (22) or ephedrine (23)), or conditions (elderly with low amplitude EEG) may affect the BIS level.

Evidence in support of a reduction in awareness under general anesthesia with BIS monitoring is derived from two sources: a randomized controlled trial in high-risk patients (24) and a nonrandomized cohort comparison with historical controls (25). Myles et al. (24) performed a randomized controlled trial of BIS monitoring in 2500 patients at high risk for intraoperative awareness (e.g., high risk cardiac surgery, impaired cardiovascular status, trauma, cesarean section, chronic benzodiazepine or opioid use, heavy alcohol intake, history of awareness). Explicit recall occurred in 0.17% (two patients) when BIS monitors were used to guide anesthesia and in 0.91% (11 patients) managed by routine clinical practice ($P < 0.02$) (24). Although very promising, it is important to realize that if only one extra patient had reported awareness in the BIS group, the difference would have no longer been statistically significant. This is particularly relevant as the end point "awareness" has no "gold standard," unlike death, myocardial infarction, or stroke. Unresolved issues included difficulties in determining "possible" compared to "definite" awareness and the optimal time to interview a patient for possible awareness.

Ekman et al. (25) compared the incidence of awareness in a prospective cohort of 5057 patients where BIS was used to guide anesthetic administration with the incidence in a historical control group of 7826 patients (10). Explicit recall occurred in 0.04% of the BIS patients versus 0.18% of the historical controls ($P < 0.038$). Again, if just one extra patient were classified with awareness in the BIS-monitored cohort and one less in the historical cohort, the difference would not have been statistically significant. In addition, anesthetic practice may have been changed unrelated to BIS monitoring, as well as affected by the "Hawthorne effect" (people perform better when they know they are being studied). Another prospective nonrandomized cohort study ($n = 19{,}575$), which did not study BIS-guided anesthetic depth (11), found no difference in the incidence of awareness in the BIS-monitored group.

Clinicians should also note that the predictive positive and negative values of the BIS for awareness are low due to the infrequent occurrence of intraoperative awareness. The cost of monitoring all patients undergoing general anesthesia is high (26).

The ASA's Practice Advisory on Intraoperative Awareness and Brain Function Monitors

The ASA approved a practice advisory on "Intraoperative Awareness and Brain Function Monitoring" in 2005 (20). A practice advisory is a systematically developed report that is intended to assist decision-making in areas of patient care where scientific evidence is insufficient. Advisories provide a synthesis and analysis of expert opinion, clinical feasibility data, open forum commentary, and consensus surveys. Advisories are not intended as standards or guidelines. They may be adopted, modified, or rejected according to clinical needs and constraints. Each practitioner should read and be familiar with the entire document (20). There were four areas of advice:

Preoperative Evaluation

Review patient medical records for potential risk factors

- Substance use or abuse
- Previous episode of intraoperative awareness
- History of difficult intubation or anticipated difficult intubation

- Chronic pain patients on high doses of opioids
- ASA status 4–5
- Limited hemodynamic reserve

Interview patient
Determine other potential risk factors

- High risk surgery (cardiac, trauma, emergency surgery, or Cesarean delivery)
- Reduced anesthetic doses in the presence of paralysis
- Planned use of muscle relaxants during the maintenance phase of general anesthesia
- Planned use of nitrous oxide-opioid anesthesia

Patients whom the individual clinician considers to be at substantially increased risk of intraoperative awareness should be informed of the possibility of intraoperative awareness when circumstances permit.

Preinduction Phase of Anesthesia

Adhere to a checklist protocol for anesthesia machines and equipment.

Verify the proper functioning of IV access and infusion equipment.

The decision to administer a benzodiazepine prophylactically should be made on a case-by-case basis for selected patients.

Intraoperative Monitoring

Use multiple modalities to monitor depth of anesthesia

- Clinical techniques (i.e., checking for purposeful or reflex movement)
- Conventional monitoring systems (e.g., ECG, BP, HR, end-tidal anesthetic analyzer, capnography)
- Brain function monitoring is not routinely indicated.
- The decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients

Intraoperative and Postoperative Management

1. The decision to administer a benzodiazepine intraoperatively after a patient unexpectedly becomes conscious should be made on a case-by-case basis.
2. Speak with patients who report recall of intraoperative events to obtain details of the event and to discuss possible reasons for its occurrence.
3. A questionnaire or structured interview may be used to obtain a detailed account of the patient's experience.
4. Once an episode of intraoperative awareness has been reported, an occurrence report concerning the event should be completed for the purpose of quality management.
5. Offer counseling or psychological support to those patients who report an episode of intraoperative awareness.

QUALITY OF RECOVERY

Depth of anesthesia may affect the quality and side effects encountered in the recovery period. It has been shown that the use of BIS monitoring leads to less anesthetic drug utilization and faster recovery times (5,6). In a meta-analysis of randomized controlled trials of 1380 ambulatory anesthesia patients, Liu (27) reported that BIS monitoring reduced anesthetic use by 19%, reduced the risk of postoperative nausea and vomiting by 6%, but only reduced the time that patients spent in the PACU by 4 min.

Chan et al. (28) reported at the 2005 ASA meeting the findings of a study in which they assessed the effect of a device in which anesthetic depth was controlled by use of an auditory evoked potential monitor (AEP) in over 1000 patients. In the AEP group, sevoflurane and propofol doses were reduced by 29% and 16% respectively; emergence was faster and patients were discharged home earlier (6.9 ± 5.2 vs 9.1 ± 8.1 days); and the incidence of postoperative nausea and vomiting was reduced from 48% to 20%. Even more remarkable was the observation that 30 days following the surgical procedure, AEP patients rated their quality of recovery higher than the controls.

POSTOPERATIVE NEUROCOGNITIVE DYSFUNCTION

Postoperative neurocognitive dysfunction is a frequent occurrence after cardiac and noncardiac surgery. Intuitively one would suspect that lower doses of anesthetics would lead to less or attenuated postoperative neurocognitive dysfunction. However, there is a lack of peer-reviewed published data to support or refute this hypothesis.

Farag et al. (29) reported on 74 patients >50 yr of age for noncardiac surgery. The study paradigm allowed for a "LoBIS" 30–40 and a "HiBIS" 50–60 group. Deeper levels of anesthesia (e.g., low BIS) were associated with improved cognitive function on 1 out of 3 tests (29). The significance of these findings is unclear and goes against conventional wisdom. These results are preliminary and need to be corroborated by peer review and additional research.

POSTOPERATIVE MORTALITY

Two separate trials have reported an association with "deep" anesthesia (BIS level <45) and mortality. Lennmarken et al. (Anesthesiology 2003;99:A303) reported, at the 2003 ASA Annual Meeting, on mortality data in 5057 patients undergoing noncardiac surgery. The number of minutes at a BIS level of <45 was recorded and compared with local municipal mortality records. The number of minutes at a BIS level of <45 was a significant predictor of 1-yr mortality with a 19.7% increased risk for each hour spent at a BIS level <45.

In a second independent evaluation of this question, Monk et al. presented the provocative conclusion that cumulative time spent with BIS scores <45 was an

independent predictor of 1 yr mortality in patients undergoing major, noncardiac surgery (8,9). The authors conducted a prospective, observational study at a single hospital ($n = 1064$) in noncardiac patients >18 yr of age. The BIS level was recorded throughout the surgical procedure and correlated to 1-yr mortality. They observed that morality was increased by 24.4% per hour that BIS <45.

As these studies are observational in design, associations reflect correlation and not necessarily causation. In particular, unmeasured and uncontrolled variation in coexisting diseases that are highly correlated with mortality (e.g., certain types of cancer), may be the underlying cause of the increased mortality rather than depth of anesthesia.

SUMMARY

Depth of anesthesia is an important factor in the anesthetic management of patients. When considering depth of anesthesia as it relates to the risk of intraoperative awareness, the following points are key:

- Incidence of 1–2/1000
- There is the potential for serious psychological/medicolegal sequelae
- Equipment check is paramount in the prevention of intraoperative awareness
- Amnestic agents—although the evidence is lacking, the clinician may consider an amnestic as a premedicant in patients at risk for intraoperative awareness, and as a treatment when patients are lightly anesthetized
- Re-dose hypnotics in clinical situations that are at risk for intraoperative awareness (e.g., difficult airway)
- Hemodynamics are unreliable as a predictor of inadequate anesthesia
- There is no proven awareness monitor that has 100% sensitivity and specificity. Current monitors have low positive and negative predictive power for awareness
- Monitor the end-tidal anesthetic level
- Consider at least a 0.6 MAC level of a volatile anesthetic
- Neuromuscular blockers will mask an important indicator of inadequate anesthesia
- Consider a brain function monitor as an adjunct to other available indicators of anesthetic depth

When considering other outcome measures which depth of anesthesia may affect, the data is not as compelling. Monitoring depth of anesthesia may decrease anesthetic dose, enhance "fast-tracking" of patients, decrease side effects from anesthesia (e.g., PONV), and enhance the patient's quality of recovery. The effect of avoiding deep levels of anesthesia on other outcome measures such as neurocognitive dysfunction and mortality is less clear, but preliminary data suggests that avoiding deep levels of anesthesia may be a useful goal of anesthetic management.

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